REMARKS

Introduction

Claims 30-34 and 50-54 are pending. Claims 1-29 remain cancelled and claims 35-49 are cancelled herein. Applicants expressly reserve the right to pursue the cancelled claims in other applications or to request rejoinder of these claims during prosecution of this application.

Claims 30-32 and 34 have been amended herein. New claims 50-54 have been added. Support for these amendments and new claims can be found throughout the specification, for example, in the claims as filed and in paragraphs [0027], [0038], and [0069]. No new matter is believed to have been added.

Listing of Applications/Patents

Further to the Examiner's request, the following U.S. applications and patents are provided. Applicants explicitly note that providing this listing is a courtesy and **is not an express or implied admission** as to whether these applications contain similar subject matter or that these applications are relevant in any way to prosecution of the pending application.

- U.S. Pat. Appl. 11/790,216
- U.S. Pat. No. 7,223,413

Rejections under 35 U.S.C. §112

The Examiner has rejected claims 31 and 34 under 35 U.S.C. §112 as allegedly being indefinite. Applicants disagree. However, all the corrections requested in the Office Action have been made such that claim 31 is not indefinite. With respect to claim 34, the claim has been amended to recite specific concentrations. Applicants believe that the amended claims clearly

define the metes and bounds of the invention and are not indefinite.

The Examiner has also rejected claims 30-34 under 35 U.S.C. §112 as allegedly failing to enable the compositions for *in vivo* uses. Applicants disagree. However, solely to expedite prosecution, claim 30 has been amended to specify that the compositions are for controlling viability of an explanted tissue or organ. The specification, including Examples 1-4, provides data and description of uses of the claimed compositions in explanted tissue and/or organs. Thus, amended claim 30 is fully enabled as are its dependent claims by virtue of their dependency.

For at least the above reasons, Applicants respectfully assert that the rejections under 35 U.S.C. §112 have been rendered moot or overcome and withdrawal of these rejections is requested.

Rejection for Double Patenting

The Examiner has rejected claims 30 and 34 on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of U.S. Patent 6,955,814 (the '814 patent). Without acquiescing to the alleged grounds for the rejection, and solely to expedite prosecution, Applicants submit herewith a terminal disclaimer over the '814 patent. This rejection is now moot and its withdrawal is respectfully requested.

Rejection under 35 U.S.C. §102

The Examiner has rejected claims 30 and 34 under 35 U.S.C. §102(b) as allegedly being anticipated by WO 00/56145 (the '145 publication), in light of Segal *et al.* (Segal). Applicants disagree for at least the reasons below.

A. The '145 Publication and/or Segal do not disclose the claimed composition for use in an explanted tissue or organ

These two documents do not disclose the use of the claimed compositions, which include a sodium hydrogen exchange inhibitor, in explanted tissue or organs. Claims 30 and 50 are directed to compositions for controlling viability of an explanted tissue or organ. The '145 publication is directed to the arrest, preservation, and/or protection of organs in a living patient, not controlling the viability of explanted tissue or organs. The '145 publication provides examples of situations its compositions are useful for, including, use of the compositions during open-heart surgery, cardiovascular diagnosis, or therapeutic intervention. See pg. 1, ll. 3-6. Other non-explanted tissue or organ uses are also reflected in the Examples provided in the '145 publication, for example, the portion of Example 5 entitled "Summary of Adenosine and Lignocaine During a Heart Attack *in vivo*." See, e.g., pgs. 45-46. These are distinct compositions for different uses than the claimed compositions. Segal does not cure the deficiencies of the '145 publication because it also does not address using the claimed compositions in explanted tissue or organs and instead uses a different composition in highly cultured A6 cells grown on permeable supports. Therefore, the '145 publication, even in view of Segal, does not anticipate claims 30 or 50.

B. The '145 Publication and/or Segal do not disclose, either expressly or inherently, all elements of the claimed compositions

The '145 publication, even in view of Segal, does not teach all the components of the claimed compositions. The independent claims, as amended, require a potassium channel opener or adenosine receptor agonist; a local anaesthetic; and a sodium hydrogen exchange inhibitor. Neither Segal nor the '145 publication, even in view of one another, expressly

disclose including a sodium hydrogen exchange inhibitor in compositions for use in controlling viability of an explanted tissue or organ.

To remedy this deficiency, the Examiner asserts that the verapamil in the '145 publication, as explained in Segal, inherently has multiple functions, including inhibition of transepithelial Na^+ transport. Thus, the inclusion of verapamil for a different use in the '145 publication, by virtue of this inherent function, allegedly also meets the limitation in claim 30 requiring a sodium hydrogen exchange inhibitor.

As MPEP section 2112 sets forth, the burden rests on the Examiner to establish inherency. Importantly, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." See MPEP section 2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis added). The MPEP continues stating that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Finally, the MPEP specifies that "[i]nherency, however, may not be established by probabilities or possibilities. **The mere fact that a certain thing may result from a given set of circumstances is not sufficient.**' " *Id.* citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

The '145 publication, even in view of the Segal document, does not demonstrate that verapamil acts as a sodium hydrogen exchange inhibitor in explanted tissue, nor does it demonstrate that this activity always, and thus, inherently occurs. Segal deals with the effects of verapamil in the A6 cell line. See Segal pg. 765, col. 2. Accordingly, the researchers

conclude that their results are applicable to A6 cells, not all sodium transport, when they state "[w]e conclude that verapamil inhibits transepithelial Na+ transport in A6 cells by blocking ENaC." See Abstract of Segal. Also, A6 cells contain ENaC; a specific channel that is not considered a sodium hydrogen exchanger. The claims, however, are directed to compositions comprising a sodium hydrogen exchanger not an ENaC inhibitor.

The Segal researchers further realize the narrow scope of their findings when they point out in figure 4 that the function of verapamil is pH dependent. The pH of specific organs can vary, for example, Segal notes that the pH at the distal tubule can be as low as 5.5. See Segal at 768, col. 2. To the contrary, most cells exist at a pH of 7.2-7.4 in the body. Thus, when presented with the pH dependency of verapamil's effect within the A6 cells used in Segal, it is improper for the Examiner to conclude that any inhibition of transepithelial sodium transport shown in Segal would inherently occur in explanted organs as the claims require.

In conclusion, the Examiner's broad assertion that Segal demonstrates a dual functionality of verapamil is flawed. Factors such as the type of channel present in the cells and pH will influence whether verapamil behaves as the Examiner asserts. There is simply no evidence in the record that verapamil is a sodium hydrogen exchange inhibitor that will always, and therefore inherently, have the claimed effect in an explanted tissue or organ. Therefore, the Examiner has not met the burden for establishing an inherency argument and is instead dealing with possibilities rather than certainties, as the MPEP and case law require.

C. The '145 Publication and/or Segal do not disclose compositions containing the three different components of claim 50

Further, with respect to claim 50, the '145 publication, even in view of Segal, does not disclose the use of a potassium channel opener or adenosine receptor agonist; a local

anaesthetic; and a sodium hydrogen exchange inhibitor, where each of the three compounds are different. For this additional reason, claim 50 is not anticipated.

For at least the above reasons, the '145 publication, even in view of Segal, does not expressly or inherently anticipate claims 30 or 50, or their dependant claims by virtue of their dependency on either claim 30 or 50. The rejection under 35 U.S.C. §102(b) is improper and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

The Examiner has rejected claims 30-34 under 35 U.S.C. §103(a) as allegedly being obvious over the '145 publication in combination with U.S. Pat. No. 5,693,462 issued to Raymond (the '462 patent). Applicants disagree for at least the reasons below.

None of these documents provide evidence or suggest that the inclusion of a sodium hydrogen exchange inhibitor would be desirable or successful in the distinct formulations disclosed in the '145 publication. As discussed above, the '145 publication is not directed to the claimed compositions for use in explanted tissue or organs. The '462 patent, in contrast, is purportedly directed to organ transplant solutions. See Abstract of the '462 patent. These are distinct medical situations which require precisely designed preserving solutions to be successful clinically. Thus, one of skill in the art would not be motivated to mix and match ingredients between solutions as the Examiner has done.

Moreover, the addition of new components to a composition, e.g. the addition of a sodium hydrogen exchange inhibitor to the compositions of the '145 publication, can be potentially unsafe and at the least the success of such an addition cannot be predicted. The compositions of the '462 patent are directed to combinations of ions (e.g., magnesium), in combination with amiloride, adenosine and many other ingredients. See col. 4, lines 35-63 and Examples 1-3.

However, none of these formulations demonstrate that a sodium hydrogen exchange inhibitor could be safely or successfully incorporated into compositions containing a potassium channel opener or agonist and/or an adenosine receptor agonist in combination with a local anesthetic. The co-administration of a local anesthetic in combination with a sodium hydrogen exchange inhibitor and a potassium channel opener is demonstrated to be unexpectedly successful for controlling the viability of an explanted tissue or organ in the Applicant's disclosure, but not in the prior art.

For at least the reasons above, one of skill in the art would not have been motivated to add amiloride into the compositions disclosed in the '145 publication nor would they have expected the addition of amiloride to short term organ arrest compositions using a local anesthetic to have been successful. Accordingly, the claimed invention is not obvious and the rejection under 35 U.S.C.§103(a) should be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Accordingly, Applicants request that the Examiner issue a Notice of Allowance indicating the allowability of all the claims and that the application be passed to issue.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Matthew E. Kelley
Registration No. 55,887
VENABLE
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 344-4000
Telefax: (202) 344-8300

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